JUL 21 2008

510(k) Summary of Safety and Effectiveness

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

The assigned 510(k) number is: K063662 .

1. Establishment:

Response Biomedical Corporation
1781 – 75th Avenue W.
Vancouver, British Columbia
Canada, V6P 6P2

Tel: (604) 456-6010
Fax: (604) 456-6066

Contact: Ken Pilgrim
Director – Quality / Regulatory

Prepared: July 2, 2008

2. Regulatory Information:

Trade Name:	**Response Biomedical Corporation RAMP® NT-proBNP Assay**
Common Name:	NT-proBNP immunological test system
Classification Name:	NT-proBNP immunological test system
Regulation Number:	862.1117, B-type Natriuretic Peptide Test System
Classification:	Class II
Product Code:	NBC
Panel:	Clinical Chemistry (75)

3. Predicate Device:

Immunoassay:	Elecsys® proBNP, (K022516, K032646, K051382) which is currently marketed by Roche Diagnostics GmbH.
Immunoassay:	*Status*First™ CHF NT-proBNP (K051596), which is currently marketed by Nanogen, Inc.

4. Description of the Device:

The RAMP NT-proBNP Assay is a quantitative immunochromatographic test indicated for use as an *in vitro* diagnostic product used with a RAMP reader to measure N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in EDTA whole blood. Mixed EDTA whole blood is added to the sample well of the Test Cartridge which houses the immunochromatographic test strip. The red blood cells are retained in the sample pad, and the separated plasma migrates along the strip. Fluorescent-dyed latex particles coated with anti-NT-proBNP antibodies bind to NT-proBNP, if present in the sample. As the sample migrates along the strip, NT-proBNP bound particles are captured at the detection zone, and additional particles are captured at the internal standard zone.

The RAMP reader then measures the amount of fluorescence emitted by the complexes captured at the detection zone and at the internal standard zone. Using a ratio between the two fluorescence values, a quantitative reading is calculated.

5. Comparison of Technological Characteristics:

The RAMP NT-proBNP Assay, Elecsys proBNP Assay and *Status*First CHF NT-proBNP Test are all used for the quantitative measurement of NT-proBNP in human whole blood (RAMP) or plasma (Elecsys and *Status*First). All three immunoassays utilize the binding of NT-proBNP to specific antibodies. The RAMP assay measures light production from a fluorescence reaction using a fluorometer, which is directly proportional to the amount of NT-proBNP present in a patient sample. The Elecsys assay is an electrochemiluminescence immunoassay utilizing the application of voltage to an electrode inducing an emission measured by a photomultiplier, which is directly proportional to the amount of NT-proBNP present in a patient sample. The *Status*First test utilizes a biotin coupled antibody/streptavidin solid-phase chromatographic immunoassay in which the analyte concentration in the sample correlates with the intensity of the test band.

The RAMP and *Status*First assays are both quantitative immunochromatographic tests, whereas the Elecsys proBNP Assay is a quantitative sandwich immunoassay.

The Elecsys proBNP Assay utilizes two sheep polyclonal antibodies that recognize epitopes located in the N-terminal part (1-76) of proBNP (1-108). The RAMP NT-proBNP Assay utilizes one sheep polyclonal and one mouse monoclonal antibody that recognize epitopes located in the N-terminal part (1-76) of proBNP (1-108). The *Status*First test utilizes polyclonal and monoclonal antibodies to the N-terminal part (1-76) of proBNP (1-108).

The RAMP NT-proBNP Assay is for use in the central laboratory, stat-lab and point-of-care facilities, while the Elecsys proBNP Assay is for use in the central and stat laboratories. The intended location for use of the *Status*First is not indicated in the device labeling.

All three assays are indicated for use in the diagnosis and assessment of severity in individuals suspected of having congestive heart failure. All three assays may also aid in risk stratification.

A comparison between the RAMP, the Roche Elecsys and Nanogen *Status*First assays is presented in the table below.

Substantial Equivalence Comparison Table

Features/ Technical Information	Response Biomedical Corporation RAMP NT-proBNP Assay	Roche Diagnostics Elecsys proBNP Assay	Nanogen, Inc. *Status*First NT-proBNP Test
Indication for Use	The RAMP NT-proBNP Assay is a quantitative immunochromatographic test indicated for use as an *in vitro* diagnostic product used to measure N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in EDTA whole blood. Measurement of NT-proBNP aids in the diagnosis and assessment of severity in individuals suspected of having congestive heart failure and may aid in the risk stratification of patients with heart failure.	Elecsys proBNP is used as an aid in the diagnosis of individuals suspected of having congestive heart failure. The test is further indicated for the risk stratification of patients with acute coronary syndrome and congestive heart failure. The test may also serve as an aid in the assessment of increased risk of cardiovascular events and mortality in patients at risk for heart failure who have stable coronary disease.	The device is intended for use with the DXpress™ Reader to provide quantitative results as an aid in the diagnosis of CHF.
Quantitative/ Qualitative	Quantitative	Quantitative	Quantitative
Test Principle	Immunochromatographic fluorescence immunoassay	Electrochemiluminescent immunoassay	Biotin coupled antibody/streptavidin solid-phase chromatographic immunoassay
Traceability Standardization	Reference standard - purified synthetic NT-proBNP (1-76) in human serum matrix	Reference standard - purified synthetic NT-proBNP (1-76) in human serum matrix	Unknown
Antibodies Used	One sheep polyclonal and one mouse monoclonal antibody, recognizing epitopes located in the N-terminal part (1-76) of proBNP (1-108).	Two sheep polyclonal antibodies, recognizing epitopes located in the N-terminal part (1-76) of proBNP (1-108).	Polyclonal and monoclonal antibodies to the N-terminal part (1-76) of proBNP (1-108) of unknown animal origin.
Site of Use	Central laboratory, stat-lab and point-of-care facilities	Central laboratory and stat-lab	Unknown
Specimen Type	Whole blood (EDTA)	Serum and Plasma (lithium and sodium heparin, EDTA)	Plasma (EDTA)
Reported Range	27 – 22,000 ng/L	5 – 35,000 ng/L	20 – 5,000 ng/L
Test Time	15 minutes after Test Components come to room temperature	18 minutes	15 minutes after Test Device comes to room temperature
Instrument	RAMP readers	Elecsys 1010, Elecsys 2010 and MODULAR analytics E 170 family of analyzers	DXpress Reader
Assay Reagent Storage	Refrigerated (2 to 8°C); must be brought to room temperature prior to running assay.	Refrigerated (2 to 8 °C) for 12 weeks.	Refrigerated (2 to 8°C); must be brought to room temperature prior to running assay.
Stability at Room Temperature	14 days unopened; but not beyond the expiration date.	On E170 & 2010 for 8 weeks, on 1010 for 4 weeks (at 20-25°C up to 20 hours opened in total).	14 days unopened; but not beyond the expiration date.
Standard Curve	Lot specific; provided on Lot Card.	Generate with each reagent lot.	Lot specific; provided on Data Chip.

Features/ Technical Information	Response Biomedical Corporation RAMP NT-proBNP Assay	Roche Diagnostics Elecsys proBNP Assay	Nanogen, Inc. *Status*First NT-proBNP Test
Quality Controls	Provided in every Test Cartridge. Built in performance controls for routine QC requirements. Indicates sufficient sample was applied and the cartridge was inserted and read properly by the instrument. Antibody quality, system function and assay timing are checked on each assay run. An unacceptable result from the control displays an error message on the instrument.	Recommended at least once each day of use	Provided in every Test Device. The control line is an internal positive procedural control. A distinct reddish-purple control line should appear at the control position if the test is performed properly, an adequate sample volume is used, the sample and reagent are wicking on the membrane, and the reagents at the control line are reacting with the conjugate-color indicator. In addition, a clear background may be considered a negative procedural control. The Dxpress Reader will report "Control: Valid" and the test results for NT-proBNP (pBNP) when Internal Control QC is satisfied.
Liquid Control	Audit MicroFD BNP Control	Elecsys PreciControl proBNP Elecsys PreciControl Cardiac	Commercially available NT-proBNP Controls
Result Interpretation	125 pg/mL for patients 75 years and younger and 450 pg/mL for patients older than 75 years.	125 pg/mL for patients younger than 75 years and 450 pg/mL for patients 75 years and older.	Decision thresholds: Patients under 75 years of age: 125 pg/mL, Patients 75 years of age and older: 450 pg/mL. NT-proBNP results less than or equal to the decision threshold values are considered normal values representative of patients without CHF. Results greater than the above stated decision threshold values are considered abnormal and suggestive of patients with CHF.

6. Summary of Studies:

PERFORMANCE CHARACTERISTICS

Precision

The intra-assay and inter-assay precision of the RAMP NT-proBNP Assay were determined by one operator assaying duplicates of three concentrations of control material (140, 449 and 1675 ng/L NT-proBNP) twice each day over a 10-day period. The mean, standard deviation and %CV were calculated for each reported concentration of NT-proBNP. The results of this precision analysis are shown below.

Precision	NT-proBNP Standards		
NT-proBNP ng/L	140	449	1675
Within Run CV	9.4%	6.4%	5.5%
Total CV	10.3%	9.8%	8.9%

EDTA anticoagulated whole blood samples spanning the reportable range of the RAMP NT-proBNP Assay were analyzed. Ten replicate measurements were carried out by a single operator in one day. The results of twelve samples from this precision analysis are shown below.

Precision	EDTA Whole Blood Samples										
Mean NT-proBNP ng/L	52	73	113	131	161	299	2306	4051	5889	8445	19504
CV (%)	20.7	16.6	12.1	10.3	6.6	7.4	4.5	4.4	4.3	5.4	3.0

Precision in the hands of the end user was evaluated at each clinical site (N=4). Each operator performed three (3) replicates of a plasma based control product. The results are presented for each operator and across operators below:

Operator	1	2	3	4	5	6	combined
Level 1 CV (%)	9.3%	9.5%	15.5%	8.8%	11.8%		11.0
Level 2 CV (%)	3.4%	6.7%	4.4%	0.4%	12.4%	2.5%	5.0

Linearity

A high NT-proBNP antigen concentration was prepared in normal donor EDTA blood and determined to contain 21,921 ng/L NT-proBNP by assaying the sample in duplicate. The sample was serially diluted six times. Regression analysis using the method of Passing-Bablok of actual versus expected NT-proBNP concentration resulted with an R-value of 1.00, a slope of 1.06 and an offset of -1.4 ng/L. The recovery of NT-proBNP antigen at the six dilutions ranged from 101 to 120% with an average of 108%.

A low NT-proBNP antigen concentration was prepared in normal donor EDTA blood and determined to contain 264 ng/L NT-proBNP by assaying the sample in duplicate. The sample was serially diluted four times. Regression analysis using the method of Passing-Bablok of actual versus expected NT-proBNP concentration resulted with an R-value of 1.00, a slope of 1.06 and an offset of –2.0 ng/L. The recovery of NT-proBNP antigen at the four dilutions ranged from 85 to 110% with an average of 100%

Hook Effect

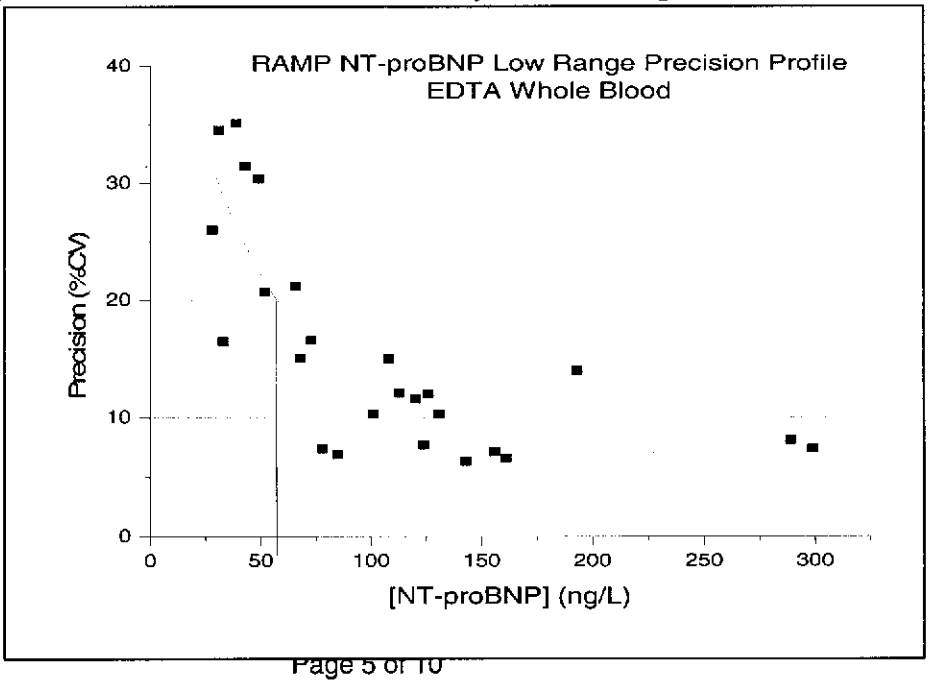
There is no high dose hook effect in the RAMP NT-proBNP Assay up to the highest level tested (350,000 ng/L NT-proBNP).

Limits of Detection and Quantitation

Following CLSI EP-17A, limit of detection (LoD) was determined to be 34 ng/L, the limit of blank (LoB) was calculated as the 95th percentile from forty replicates of a blank sample run using the RAMP NT-proBNP Assay and was determined to be 27 ng/L..

NT-proBNP levels in excess of 22,000 ng/L are reported as greater than (>) 22,000 ng/L.

The limit of quantitation (LoQ) is defined as the NT-proBNP level at which the test method displays a particular coefficient of variation (%CV). As shown below, the 20% LoQ for the RAMP NT-proBNP Assay was determined from whole blood analyses to be 57 ng/L.



Analytical Specificity

Human anti-mouse antibodies (HAMA) and Rheumatoid Factor (RhF) appear to have minimal cross-reactivity with the RAMP NT-proBNP Assay. Possible cross-reactivity of other substances was evaluated by spiking different concentrations of the potential cross-reactants into EDTA blood which had NT-proBNP added. No cross reactivity was observed with the RAMP NT-proBNP assay up to the maximum levels tested for the compounds listed in the following table.

Compound	Concentration	Compound	Concentration	Compound	Concentration
ANP_{28}	3.1 µg/mL	$preproANP_{104-123}$	1 ng/mL	Endothelin	20 ng/L
BNP_{32}	3.5 µg/mL	Aldosterone	0.6 ng/mL	Arg-Vasopressin	1 ng/mL
CNP_{22}	2.2 µg/mL	Angiotensin I	0.6 ng/mL	Renin	50 ng/mL
$preproANP_{26-55}$	3.5 µg/mL	Angiotensin II	0.6 ng/mL	Andrenomedullin	1 ng/mL
$preproANP_{56-92}$	1 ng/mL	Angiotensin III	1 ng/mL	Urodilatin	3.5 µg/mL

Interference

Potentially interfering substances were evaluated by spiking different concentrations of potential interferents into EDTA whole blood with NT-proBNP added to provide levels of 125 and 450 ng/L. Different blood samples were used for each potential interferent with an average difference of less than 10% from the unspiked samples observed in each case. The therapeutic compounds tested (at concentrations up to and including those indicated) are listed in the following table:

Compound	Concentration	Compound	Concentration
Acetaminophen	20 mg/dL	Furosemide	6 mg/dL
Acetylsalicylic acid	100 mg/dL	Hydralazine	20 µg/mL
Allopurinol	4 mg/dL	Hydrochlorothiazide	20 µg/mL
Amiodarone	20 µg/mL	Indomethacin	40 µg/mL
Amiodipine Besylate	4 µg/mL	Insulin	120 µU/mL
Ampicillin sodium salt	100 mg/dL	Isosorbide Dinitrate	15 mg/dL
Ascorbic acid	30 mg/dL	Lisinopril	4 mg/dL
Atenolol	1 mg/dL	Methyldopa	2.5 mg/dL
Caffeine	10 mg/dL	Metoprolol Tartrate	2 mg/dL
Captopril	15 mg/dL	Nicotine	2 mg/dL
Carvedilol	5 mg/dL	Nifedipine	6 mg/dL
Chloramphenicol	25 mg/dL	Nitroglycerin	19.2 mg/dL
Clopidogrel Hydrogensulfate	7.5 mg/dL	Oxytetracycline	100 µg/mL
Cyclosporin A	0.5 mg/dL	Probenecid	600 µg/mL
Diclofenac	60 µg/mL	Propranolol	0.2 mg/dL
Digitoxin	0.03 mg/dL	Quinidine	20 µg/mL
Digoxin	0.05 mg/dL	Simvastatin	4 mg/dL
Diltiazem	120 µg/mL	Theophylline	100 mg/dL
Phenytoin	10 mg/dL	Trimethoprim	60 µg/mL
Dipyridamole	30 µg/mL	Verapamil	16 mg/dL
Enalapril Maleate	4 mg/dL	Warfarin	20 µg/mL
Erythromycin	20 mg/dL		

Hemoglobin, triglyceride, bilirubin, cholesterol, and heparin at levels of very high physiological concentrations were also investigated for possible interference. No interference was observed when tested at the concentrations up to and including those shown in the following table

Compound	Concentration	Compound	Concentration
Hemoglobin	2 g/dL	Cholesterol	500 mg/dL
Triglyceride	4 g/dL	Heparin	104 IU/mL
Bilirubin	35 mg/dL		

CLINICAL EVALUATIONS OF ANALYTICAL PERFORMANCE

Method Comparison

Six hundred and ninety-nine (699) patients were enrolled in the method comparison study. The presenting population included 46% (323) subjects with hypertension, 30% (208) with shortness of breath, 22% (152) with diabetes, 14% (99) with pulmonary disorders, 12% (84) with coronary disease, 8% (56) with atrial fibrillation, 4% (31) with renal failure, 19% (133) were healthy, and the remainder had diagnoses not believed to be cardiac related (hepatitis, HIV, cancer, etc.).

EDTA and heparin whole blood samples were obtained for each of these subjects. An aliquot of EDTA whole blood was used for the RAMP NT-proBNP Assay and heparinized plasma was prepared for the Roche Elecsys proBNP Assay. From these analyses it was determined that 580 samples contained between 34 ng/L (RAMP LoD) and 22,000 ng/L of NT-proBNP. Of these, 274 were diagnosed with heart failure (HF) based on individual hospital criteria (164 males and 110 females) and 306 were non-HF reference group patients (124 males and 182 females). Regression analysis data of RAMP NT-proBNP versus Elecsys proBNP using the method of Passing-Bablok is presented in the table below.

Comparative Method	Slope	Intercept (ng/L)	Correlation coefficient (R)
Roche Elecsys	0.97	19.39	0.98
95% CI	0.95 to 1.00	14.20 to 24.67	0.97 to 0.98

Clinical Sensitivity and Specificity

Clinical sensitivity and specificity were calculated using data collected from 858 subjects. Of these, 299 were diagnosed with HF using local hospital criteria, 189 individuals without HF but with potentially confounding co-morbidity (diabetes, renal insufficiency, hypertension or chronic obstructive pulmonary disease) and 370 reference individuals. This reference group includes an additional 159 subjects added from an additional clinical site without concomitant testing in the Elecsys system. Of these, 55% (87) were male and 8% (12) were more than 75 years old. None of these patients had reported co-morbidities. These subjects were healthy individuals with no clinical indications for natriuretic peptide testing.

The use of the cut-offs of 125 ng/L for ≤75 years of age and 450 ng/L for >75 years of age was evaluated for the RAMP data (N = 858; 299 with CHF) stratifying by the presence or absence of co-morbidities (diabetes, renal insufficiency, hypertension or chronic obstructive pulmonary disease).

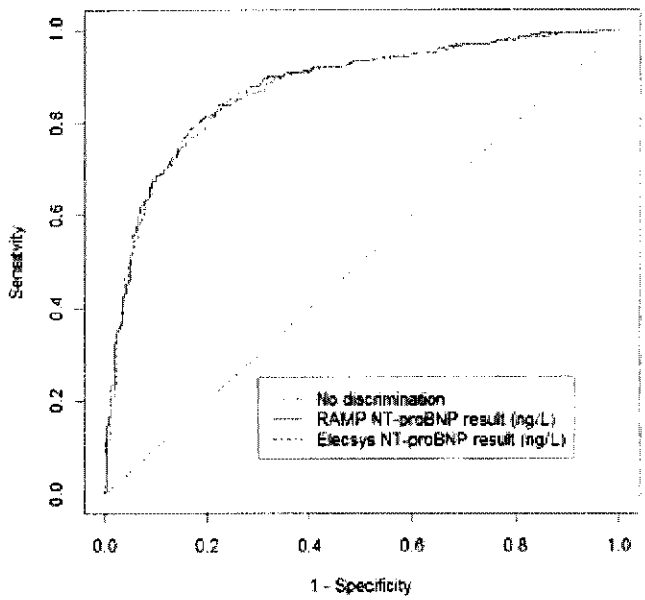
Age Stratified Sensitivity and Specificity: 125/450 ng/L by Age

CHF Patients	RAMP	RAMP
Age (years)	≤ 75	> 75
N	217	82
Sensitivity	0.89	0.99
95% CI	(0.84-0.93)	(0.92-1.0)
Non-CHF no comorbidity	RAMP	RAMP
Age (years)	≤ 75	> 75
N	340	30
Specificity	0.85	0.72
95% CI	(0.80-0.88)	(0.53-0.87)

Non-CHF with comorbidity	RAMP	RAMP
Age (years)	≤ 75	> 75
N	124	65
Specificity	0.43	0.48
95% CI	(0.43-0.52)	(0.35-0.60)

The Receiver Operator Characteristics (ROC)

The ROC analyses for both the RAMP NT-proBNP and Roche Elecsys proBNP assays for the parallel clinical study population are shown below. The additional 159 non-CHF RAMP patients are excluded from this analysis to allow direct comparison to the Elecsys system. The area under the curve (AUC) for both the RAMP NT-proBNP Assay and Elecsys proBNP assay is 0.87.



HF Population by NYHA Classification

The 299 subjects diagnosed with heart failure were evaluated using the RAMP NT-proBNP Assay. The descriptive statistics for NT-proBNP concentrations (ng/L) are presented according to NYHA Functional Classification in the table below.

All				
NYHA Class	**I**	**II**	**III**	**IV**
n	58	91	84	66
Mean	1686	2831	5737	8308
SD	3161	4356	5939	7090
Median	832	1479	3608	6628
95th percentile	5560	8104	20177	>22000
Male				
n	32	56	55	40
Mean	1737	2870	5799	8855
SD	3924	4641	6182	7612
Median	724	1318	3623	5772
95th percentile	4722	10742	21068	>22000

Female				
n	26	35	29	26
Mean	1624	2771	5618	7466
SD	1918	3921	5551	6251
Median	907	1622	3598	6937
95th percentile	5438	7306	16727	21839

Non-HF and HF Group Descriptive Statistics

The overall incidence of disease in the presenting population (n=858) included 38% (323) subjects with hypertension, 24% (208) who presented with shortness of breath, 18% (152) with diabetes, 12% (99) with pulmonary disorders, 10% (84) with coronary disease, 7% (56) with atrial fibrillation, 4% (31) with renal failure, 34% (292) were healthy, and the remainder had diagnoses not believed to be cardiac related (hepatitis, HIV, cancer, etc.).

The circulating NT-proBNP concentration was determined in 858 individuals with and without HF. The HF patients included those with prior established heart failure that were not acutely destabilized at the time of enrollment (and thus similar to those who might be tested in the outpatient setting). Patients (N=17) for whom the measured NT-proBNP level was greater than 22,000 ng/L have been excluded. The descriptive statistics for the Non-HF and HF groups are presented in the following table:

A. Non-HF Patients –RAMP Results (ng/L)

	No co-morbidity				With co-morbidity		
Age (years)	>75	≤75	ALL	Age (years)	>75	≤75	ALL
n	30	340	370	n	65	124	558
Mean	449.7	132.8	158.5	Mean	1013.0	870.5	349.4
SD	810.9	671.2	687.8	SD	1524.6	3445.1	996.0
Median	88.0	24.5	28.0	Median	512.0	185.95	66.0
95th percentile	2447.4	216.4	451.0	95th percentile	3986.0	2463.2	1543.9
% <125 ng/L		84		% <125 ng/L		44	
% < 450 ng/L	74			% < 450 ng/L	48		

B. HF Patients – RAMP Results (ng/L)

Age (years)	>75	≤75	ALL
N	80	203	283
Mean	4970.1	3133.1	3652.4
SD	5185.8	3755.0	4280.2
Median	3300.5	1735.0	2040.0
95th percentile	19005.0	11373.3	12800.0
% >125 ng/L		89	
% >450 ng/L	100		

7. Conclusion:

The RAMP NT-proBNP device demonstrates performance equivalent to that stated in the Nanogen *Status*First CHF labeling and strong correlation to the predicate Roche Diagnostics Elecsys® proBNP method.

These data show that:

- The RAMP NT-proBNP Assay has excellent sensitivity for less acute populations as might be seen in an outpatient setting when the 125/ 450 age dependent cut-offs presented in cleared NT-proBNP assay labeling is applied.
- The RAMP NT-proBNP Assay shows equivalent clinical sensitivity and specificity to that stated in the predicate Nanogen *Status*First CHF NT-proBNP labeling using these cut-offs.
- The RAMP NT-proBNP Assay has excellent correlation to the predicate Roche Diagnostics Elecsys proBNP.
- The RAMP system provides NT-proBNP results that correlate with severity of heart failure, with significantly higher values of NT-proBNP as patients from NYHA Class I through IV are examined.

RAMP®

NT-proBNP

Failure to follow RAMP NT-proBNP Assay procedures may result in invalid and/or erroneous results. Read the entire Package Insert prior to use.

NAME
RAMP® NT-proBNP Assay

INTENDED USE
The RAMP NT-proBNP Assay is a quantitative immunochromatographic test indicated for use as an *in vitro* diagnostic product used to measure N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in EDTA whole blood. Measurement of NT-proBNP aids in the diagnosis and assessment of severity in individuals suspected of having heart failure and may aid in the risk stratification of patients with heart failure.

IVD **For *in vitro* Diagnostic Use Only**

Response
Biomedical Corporation
1781 – 75th Avenue W.
Vancouver, British Columbia
Canada V6P 6P2
Tel: 001-604-456-6010 Fax: 001-604-456-6066
Email: techsupport@responsebio.com
Website: www.responsebio.com

Printed in Canada
Response Biomedical Corporation

CE

BACKGROUND AND INTRODUCTION

Heart failure (HF) is a chronic, progressive disease in which the heart muscle weakens and its function becomes impaired, thus impeding the heart's ability to pump enough blood to support the body's metabolic demands. When cardiac muscle is stretched, such as with elevated ventricular filling pressure, the inactive prohormone B-type natriuretic peptide (proBNP) is released and rapidly cleaved into physiologically active BNP and the N-terminal fragment NT-proBNP.[1] Natriuretic peptides can be used for the diagnosis of clinical problems associated with left ventricular dysfunction.[2] The advent of testing for BNPs has improved the ability of physicians to make a qualified diagnosis of heart failure and to monitor the success of treatment.[3] Being able to test the levels of NT-proBNP in patient blood samples is very useful as these levels are indicative of the degree of HF, and when combined with clinical judgment they provide superior diagnostic performance than clinical judgment alone.[4,5] NT-proBNP has been used for risk stratification of patients with acute coronary syndrome and HF.[6,7,8] It has also been shown to aid in the assessment of increased risk of cardiovascular events and mortality in patients at risk for HF who have stable coronary artery disease.[9,10,11]

Point-of-care (POC) or "near-patient" testing allows for diagnostic assays to be performed at the site of patient care delivery such as the emergency room (ER), chest pain evaluation center, or intensive care unit (ICU). Compared with centralized laboratory testing, POC testing provides for rapid clinical decision making by reducing the time spent ordering tests and transporting samples, as well as retrieving data.

PRINCIPLES OF THE TEST

The RAMP NT-proBNP Assay is a quantitative immunochromatographic test for the determination of NT-proBNP in EDTA whole blood. EDTA whole blood is mixed with buffer and antibody-coated, labeled particles, and applied into the sample well of the Test Cartridge. The red blood cells are retained in the sample pad, and the separated plasma migrates along the strip. Fluorescent-dyed particles coated with anti-NT-proBNP antibodies bind to NT-proBNP, if present in the sample. As the sample migrates along the strip, NT-proBNP bound particles are captured at the detection zone, and excessive fluorescent-dyed particles are captured at the internal standard zone.

The RAMP reader then measures the amount of fluorescence emitted by the complexes bound at the detection zone and at the internal standard zone. Using a ratio between the two fluorescence values, a quantitative reading is calculated. For further information on the use of the RAMP reader refer to the Operator's Manual.

EQUIPMENT, REAGENTS, MATERIALS

Materials Provided	Amount
Pouches containing one each RAMP NT-proBNP Test Cartridge and Assay Tip	25
RAMP NT-proBNP Sample Buffer Vials	25
Transfer Device	1
Lot Card	1
Package Insert	1

Equipment and Material required, but not provided	Equipment recommended, but not required
RAMP Instrument	Printer and accessories
	Barcode scanner
	PC with RS-232 connector
	Commercial Quality Control Material

Reagents

- The RAMP NT-proBNP Assay kit contains all the reagents necessary for the quantification of NT-proBNP in EDTA whole blood using the RAMP reader.
- The RAMP NT-proBNP Sample Buffer contains phosphate buffer, animal protein, surfactant, and ProClin® 300 / ProClin® 950 as preservatives.
  ProClin is a registered trademark of Rohm and Haas Company.

WARNINGS AND PRECAUTIONS

- The device contains material of animal origin and should be handled as a potential biohazard.
- ProClin is a potential skin sensitizer. Avoid spilling or splashing reagents containing ProClin on skin or clothing. In case of contact, thoroughly flush with water.
- Use appropriate precautions in the collection, handling, storage and disposal of blood specimens, including prepared blood specimens, and used kit contents.
  (Refer to institutional guidelines for biological waste management.)
- Discard and do not use any visibly damaged cartridges, or the contents of any Cartridge/Assay Tip pouch with a damaged seal.
- Do not use kit contents after the "Use By" date.
- Do not mix components from different kits.
- The RAMP NT-proBNP Test Cartridge, Assay Tip, and Sample Buffer Vial should be discarded after a single-use. Do not reuse.
- Dispose of unpouched, unused Test Cartridges and Assay Tips within 60 minutes.
- Sample/Buffer mixture must be applied to cartridge sample well only.
- Blood samples that show gross hemolysis may interfere with the test and cause erroneous results. If this occurs, another blood sample should be obtained and tested.
- The following symbols are used on the kit packaging:

Symbol	Definition
LOT	Batch Code
REF	Reference Number
	Use By
	Do Not Reuse
	Consult Instructions For Use
	Caution, Consult Accompanying Documents
	Storage Temperature

NOTE: Do not insert a Test Cartridge that is externally wet with blood or other liquid into the RAMP reader, as this may cause contamination or damage to the reader.

LIMITATIONS OF PROCEDURE

- Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies. In addition, other heterophilic antibodies may be present in patient samples. Such specimens may show either falsely elevated or depressed values when tested with immunoassays. The RAMP NT-proBNP Assay has been formulated to reduce the effects of heterophilic antibodies: however results from patients known to have such antibodies should be interpreted with caution.
- Blood specimens using anti-coagulants other than EDTA (e.g. heparin) and serum have not been evaluated, and should not be used.
- A test result that is inconsistent with the clinical signs and symptoms should be interpreted with caution.
- Functions such as technical or procedural errors, or the addition of substances not evaluated for may interfere with the RAMP NT-proBNP Assay.

The results obtained from the use of this product should be used only as an adjunct to other diagnostic procedures and information available to the physician.

STORAGE INSTRUCTIONS

The Test Cartridges and Sample Buffer Vials should be stored at 2 - 8°C. Prior to sample preparation, components should be removed from the refrigerator and allowed to equilibrate to room temperature for at least 15 minutes. Once removed from refrigeration the components are stable for up to 14 days when stored at room temperature (15 - 25°C), but not beyond the expiration date printed on the pouch. If the test is not used on the same day it is removed from refrigeration, use a permanent marker to write the date of removal from the refrigerator and the discard date on the foil pouch and sample buffer vial and/or the kit box.

NOTE: Do Not Freeze.

SPECIMEN COLLECTION AND PREPARATION

Testing should be completed within 2 hours of phlebotomy. However, if this is not possible, the EDTA whole blood can be stored for up to 2 days at 2 - 8°C.

NOTES: The sample should be well-mixed before use.
Use only EDTA whole blood. Do not use heparinized whole blood, or plasma, or serum.
Do not use samples that have been frozen

CALIBRATION PROCEDURES

Each RAMP NT-proBNP kit includes a Lot Card that is individually packaged in an anti-static pouch. The Lot Card provides all calibration information specific to the kit Test Cartridge lot, including lot number, expiration date, and standard curve information. For further details on loading lot-specific information, see the reader Operator's Manual. No additional calibration, beyond insertion of the Lot Card, is necessary. This operation is required only once per Assay kit lot.

SET-UP

If not previously done, remove the Lot Card for this kit lot from its pouch and insert it into the Lot Card slot on the RAMP instrument. Once the Lot Card information has been uploaded, return the Lot Card to its pouch.

WARNING: Avoid touching the contacts at the end of the Lot Card.

⚠ For additional information on the operation of the RAMP reader, please refer to the Operator's Manual.

SAMPLE ANALYSIS PROCEDURE

NOTE: Prior to sample preparation, remove all necessary components from refrigeration and allow to equilibrate to room temperature for at least 15 minutes.

You will need the Transfer Device and for <u>each</u> sample being tested, one Sample Buffer Vial and a pouch containing one Test Cartridge and one Assay Tip.

1. Place the Sample Buffer Vial upright on a clean, dry, level surface or in a sample vial holder.
2. Open a pouch containing one NT-proBNP Test Cartridge and one NT-proBNP Assay Tip. Place the Test Cartridge on a clean, dry, level surface.
3. Firmly attach the Assay Tip to the supplied Transfer Device.
4. Ensure that the EDTA whole blood sample is well mixed (by inversion). Remove the cap from the Sample Buffer Vial.
5. Fully depress the Transfer Device plunger and insert the Assay Tip into the blood sample. **<u>Do not prime or rinse the Assay Tip in the blood sample.</u>**
6. Gently release the plunger to fill the Assay Tip and immediately transfer the Assay Tip into the Sample Buffer Vial close to, but not touching the bottom of the Vial. **Do not press against the bottom of the Vial as this may block the Tip.**

7. Mix the sample **slowly** by pressing and releasing the plunger 10 times (2 seconds per cycle), taking care each time to eject entire sample into the Vial and to draw only liquid and no air into the Assay Tip. This will prevent foaming.
8. Position the filled Assay Tip directly over the sample well of the Test Cartridge and fully depress the plunger to dispense the mixed blood sample into the sample well. (Disregard any remaining droplet in the Assay Tip.) Dispose of used Assay Tip and Sample Buffer Vial according to local biohazard procedures.
9. Immediately (within 30 seconds) insert the Test Cartridge into the reader, and then press until firm resistance is felt. Delay will lead to an error message.
10. **Do not insert a Test Cartridge that is externally wet with blood or other liquid into the RAMP reader, as this may cause contamination or damage to the reader.**
11. Test result is complete approximately 15 minutes from Test Cartridge insertion.
12. Record the result.

⚠ For additional information on printing and/or uploading results, please refer to the Operator's Manual.

13. Remove the used Test Cartridge when prompted to do so by the instrument display. Dispose of the used Test Cartridge according to local biohazard procedures.

QUALITY CONTROL

System Quality Control (QC)

⚠ Refer to the reader Operator's Manual for full details on quality control measures and troubleshooting.

- The instrument has error checking and self-diagnostic functions that assure procedural control. These include algorithms and measurements used to confirm acceptable operator technique, sample handling, and assay performance.
- If a problem is detected, a message is displayed. Contact Response Biomedical Technical Support (604-219-6119) for assistance.
- Valid results are displayed only after all performance requirements have been met.

Procedural Controls

The RAMP NT-proBNP Assay has built in (procedural) controls. Each Test Cartridge has an internal standard zone that is scanned as part of the test protocol to ensure proper sample flow. Control limits for each lot of Test Cartridges are established during the manufacturing process and are incorporated in the specific Lot Card. If a control result does not meet specifications, the sample result is not reported and a message is displayed.

External Quality Control

- It is recommended that two levels of quality control material be run in the RAMP NT-proBNP Assay upon receipt of a new lot number or shipment of reagent and in conformance with federal, state and local requirements for quality control testing.
- To run a QC sample, follow the instructions under the SAMPLE ANALYSIS PROCEDURE section. Treat the control as a whole blood sample.

Test Run Messages

When the RAMP reader is unable to continue a specific task it will emit an audio alarm and display a message.

⚠ Refer to the Operator's Manual Troubleshooting Guide section for a full description of all Messages. If repeated tests give unexpected or inconsistent results, contact our Technical Support for assistance.

PERFORMANCE CHARACTERISTICS

Precision

The intra-assay and inter-assay precision of the RAMP NT-proBNP Assay were determined by one operator assaying duplicates of three concentrations of control material (140, 449 and 1675 ng/L NT-proBNP) twice each day over a 10-day period. The mean, standard deviation and %CV were calculated for each reported concentration of NT-proBNP. The results of this precision analysis are shown below.

Precision	NT-proBNP Standards		
NT-proBNP ng/L	140	449	1675
Within Run CV	9.4%	6.4%	5.5%
Total CV	10.3%	9.8%	8.9%

EDTA anticoagulated whole blood samples spanning the reportable range of the RAMP NT-proBNP Assay were analyzed. Ten replicate measurements were carried out by a single operator in one day. The results of twelve samples from this precision analysis are shown below.

Precision	EDTA Whole Blood Samples										
Mean NT-proBNP ng/L	52	73	113	131	161	299	2306	4051	5889	8445	19504
CV (%)	20.7	16.6	12.1	10.3	6.6	7.4	4.5	4.4	4.3	5.4	3.0

Precision in the hands of the end user was evaluated at each clinical site (N=4). Each operator performed three (3) replicates of a plasma based control product. The results are presented for each operator and across operators below:

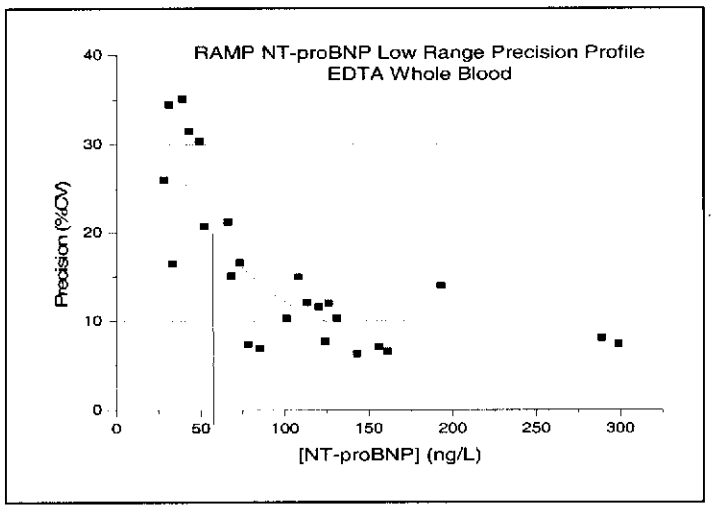
Operator	1	2	3	4	5	6	combined
Level 1 CV (%)	9.3%	9.5%	15.5%	8.8%	11.8%		11.0
Level 2 CV (%)	3.4%	6.7%	4.4%	0.4%	12.4%	2.5%	5.0

Limits of Detection and Quantitation

Following CLSI EP-17A, limit of detection (LoD) was determined to be 34 ng/L, the limit of blank (LoB) was calculated as the 95th percentile from forty replicates of a blank sample run using the RAMP NT-proBNP Assay and was determined to be 27 ng/L..

NT-proBNP levels in excess of 22,000 ng/L are reported as greater than (>) 22,000 ng/L.

The limit of quantitation (LoQ) is defined as the NT-proBNP level at which the test method displays a particular coefficient of variation (%CV). As shown below, the 20% LoQ for the RAMP NT-proBNP Assay was determined from whole blood analyses to be 57 ng/L.



Hook Effect
There is no high dose hook effect in the RAMP NT-proBNP Assay up to the highest level tested (350,000 ng/L NT-proBNP).

Linearity
A high NT-proBNP antigen concentration was prepared in normal donor EDTA blood and determined to contain 21,921 ng/L NT-proBNP by assaying the sample in duplicate. The sample was serially diluted six times. Regression analysis using the method of Passing-Bablok of actual versus expected NT-proBNP concentration resulted with an R-value of 1.00, a slope of 1.06 and an offset of -1.4 ng/L. The recovery of NT-proBNP antigen at the six dilutions ranged from 101 to 120% with an average of 108%.

A low NT-proBNP antigen concentration was prepared in normal donor EDTA blood and determined to contain 264 ng/L NT-proBNP by assaying the sample in duplicate. The sample was serially diluted four times. Regression analysis using the method of Passing-Bablok of actual versus expected NT-proBNP concentration resulted with an R-value of 1.00, a slope of 1.06 and an offset of –2.0 ng/L. The recovery of NT-proBNP antigen at the four dilutions ranged from 85 to 110% with an average of 100%.

Analytical Specificity
Human anti-mouse antibodies (HAMA) and Rheumatoid Factor (RhF) appear to have minimal cross-reactivity with the RAMP NT-proBNP Assay. Possible cross-reactivity of other substances was evaluated by spiking different concentrations of the potential cross-reactants into EDTA blood which had NT-proBNP added. No cross reactivity was observed with the RAMP NT-proBNP Assay up to the maximum levels tested for the compounds listed in the following table.

Compound	Concentration	Compound	Concentration	Compound	Concentration
ANP_{28}	3.1 µg/mL	$preproANP_{104-123}$	1 ng/mL	Endothelin	20 ng/L
BNP_{32}	3.5 µg/mL	Aldosterone	0.6 ng/mL	Arg-Vasopressin	1 ng/mL
CNP_{22}	2.2 µg/mL	Angiotensin I	0.6 ng/mL	Renin	50 ng/mL
$preproANP_{26-55}$	3.5 µg/mL	Angiotensin II	0.6 ng/mL	Andrenomedullin	1 ng/mL
$preproANP_{56-92}$	1 ng/mL	Angiotensin III	1 ng/mL	Urodilatin	3.5 µg/mL

Interference
Potentially interfering substances were evaluated by spiking different concentrations of potential interferents into EDTA whole blood with NT-proBNP added to provide levels of 125 and 450 ng/L. Different blood samples were used for each potential interferent with an average difference of less than 10% from the unspiked samples observed in each case. The therapeutic compounds tested (at concentrations up to and including those indicated) are listed in the following table:

Compound	Concentration	Compound	Concentration
Acetaminophen	20 mg/dL	Furosemide	6 mg/dL
Acetylsalicylic acid	100 mg/dL	Hydralazine	20 µg/mL
Allopurinol	4 mg/dL	Hydrochlorothiazide	20 µg/mL
Amiodarone	20 µg/mL	Indomethacin	40 µg/mL
Amiodipine Besylate	4 µg/mL	Insulin	120 µU/mL
Ampicillin sodium salt	100 mg/dL	Isosorbide Dinitrate	15 mg/dL
Ascorbic acid	30 mg/dL	Lisinopril	4 mg/dL
Atenolol	1 mg/dL	Methyldopa	2.5 mg/dL
Caffeine	10 mg/dL	Metoprolol Tartrate	2 mg/dL
Captopril	15 mg/dL	Nicotine	2 mg/dL
Carvedilol	5 mg/dL	Nifedipine	6 mg/dL
Chloramphenicol	25 mg/dL	Nitroglycerin	19.2 mg/dL
Clopidogrel Hydrogensulfate	7.5 mg/dL	Oxytetracycline	100 µg/mL
Cyclosporin A	0.5 mg/dL	Probenecid	600 µg/mL
Diclofenac	60 µg/mL	Propranolol	0.2 mg/dL

Compound	Concentration	Compound	Concentration
Digitoxin	0.03 mg/dL	Quinidine	20 µg/mL
Digoxin	0.05 mg/dL	Simvastatin	4 mg/dL
Diltiazem	120 µg/mL	Theophylline	100 mg/dL
Phenytoin	10 mg/dL	Trimethoprim	60 µg/mL
Dipyridamole	30 µg/mL	Verapamil	16 mg/dL
Enalapril Maleate	4 mg/dL	Warfarin	20 µg/mL
Erythromycin	20 mg/dL		

Hemoglobin, triglyceride, bilirubin, cholesterol, and heparin at levels of very high physiological concentrations were investigated for possible interference. No interference was observed when tested at the concentrations up to and including those shown in the following table:

Compound	Concentration	Compound	Concentration
Hemoglobin	2 g/dL	Cholesterol	500 mg/dL
Triglyceride	4 g/dL	Heparin	104 IU/mL
Bilirubin	35 mg/dL		

CLINICAL EVALUATIONS OF ANALYTICAL PERFORMANCE

Method Comparison

Six hundred and ninety-nine (699) patients were enrolled in the clinical evaluation. The presenting population included 46% (323) with hypertension, 30% (208) who presented with shortness of breath, 22% (152) with diabetes, 14% (99) with pulmonary disorders, 12% (84) with coronary disease, 8% (56) with atrial fibrillation, 4% (31) with renal failure, 19% (133) were healthy, and the remainder had diagnoses not believed to be cardiac related (hepatitis, HIV, cancer, etc.). EDTA and heparin whole blood samples were obtained for each of these subjects.

EDTA and heparin whole blood samples were obtained for each of these subjects. An aliquot of EDTA whole blood was used for the RAMP NT-proBNP Assay and heparinized plasma was prepared for the Roche Elecsys proBNP Assay. From these analyses it was determined that 580 samples contained between 34 ng/L (RAMP LoD) and 22,000 ng/L NT-proBNP. Of these, 274 were diagnosed with heart failure (HF) based on individual hospital criteria (164 males and 110 females) and 306 were non-HF reference group patients (124 males and 182 females). Regression analysis data of RAMP NT-proBNP versus Elecsys proBNP using the method of Passing-Bablok is presented in the table below.

Comparative Method	Slope	Intercept (ng/L)	Correlation coefficient (R)
Roche Elecsys	0.97	19.39	0.98
95% CI	0.95 to 1.00	14.20 to 24.67	0.97 to 0.98

Clinical Sensitivity and Specificity

Clinical sensitivity and specificity were calculated using data collected from 858 subjects. Of these, 299 were diagnosed with HF using local hospital criteria, 189 individuals without HF but with potentially confounding co-morbidity (diabetes, renal insufficiency, hypertension or chronic obstructive pulmonary disease) and 370 reference individuals. This reference group includes an additional 159 subjects added from an additional clinical site without concomitant testing in the Elecsys system. Of these, 55% (87) were male and 8% (12) were more than 75 years old. None of these patients had reported co-morbidities. These subjects were healthy individuals with no clinical indications for natriuretic peptide testing.

The use of the cut-offs of 125 ng/L for ≤75 years of age and 450 ng/L for >75 years of age was evaluated across all patients stratifying by the presence or absence of co-morbidities (diabetes, renal

insufficiency, hypertension or chronic obstructive pulmonary disease). Sensitivity and specificity are shown in the following table.

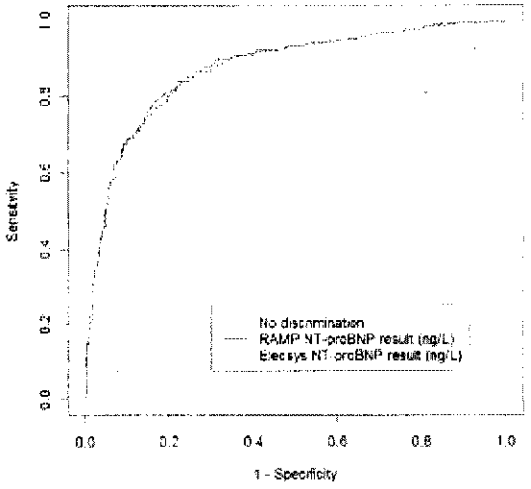
Age Stratified Sensitivity and Specificity: 125/450 ng/L for Ages ≤ 75 / >75

CHF Patients		
Age (years)	**≤ 75**	**> 75**
N	217	82
Sensitivity	0.89	0.99
95% CI	(0.84-0.93)	(0.92-1.0)
Non-CHF no comorbidity*		
Age (years)	**≤ 75**	**>75**
N	340	30
Specificity	0.85	0.72
95% CI	(0.80-0.88)	(0.53-0.87)
Non-CHF with comorbidity		
Age (years)	**≤ 75**	**>75**
N	124	65
Specificity	0.43	0.48
95% CI	(0. 43-0.52)	(0.35-0.60)

* includes additional 159 healthy subjects

Receiver Operator Characteristic (ROC) Analyses

The ROC analyses for both the RAMP NT-proBNP and Roche Elecsys proBNP assays for the clinical study population are shown below. The additional 159 patients without Elecsys results were excluded from this comparison. The area under the curve (AUC) for both the RAMP NT-proBNP Assay and Elecsys proBNP assays is 0.87.



CHF Population by NYHA Classification

The 299 subjects diagnosed with heart failure were evaluated using the RAMP NT-proBNP Assay. The descriptive statistics for NT-proBNP concentrations are presented according to NYHA Functional Classification in the table below.

All				
NYHA Class	I	II	III	IV
n	58	91	84	66
Mean	1686	2831	5737	8308
SD	3161	4356	5939	7090
Median	832	1479	3608	6628
95th percentile	5560	8104	20177	>22000
Male				
n	32	56	55	40
Mean	1737	2870	5799	8855
SD	3924	4641	6182	7612
Median	724	1318	3623	5772
95th percentile	4722	10742	21068	>22000
Female				
n	26	35	29	26
Mean	1624	2771	5618	7466
SD	1918	3921	5551	6251
Median	907	1622	3598	6937
95th percentile	5438	7306	16727	21839

Non-HF and HF Group Descriptive Statistics

The overall incidence of disease in the presenting population (n=858) included 38% (323) subjects with hypertension, 24% (208) who presented with shortness of breath, 18% (152) with diabetes, 12% (99) with pulmonary disorders, 10% (84) with coronary disease, 7% (56) with atrial fibrillation, 4% (31) with renal failure, 34% (292) were healthy, and the remainder had diagnoses not believed to be cardiac related (hepatitis, HIV, cancer, etc.).

The circulating NT-proBNP concentration was determined in 858 individuals with and without HF. The HF patients included those with prior established heart failure that were not acutely destabilized at the time of enrollment (and thus similar to those who might be tested in the outpatient setting). Patients (N=17) for whom the measured NT-proBNP level was greater than 22,000 ng/L have been excluded. The descriptive statistics for the Non-HF with and without co-morbidities and the HF groups are presented in the following tables:

A. Non-HF Patients –RAMP Results (ng/L)

	No co-morbidity				With co-morbidity		
Age (years)	>75	≤75	ALL	Age (years)	>75	≤75	ALL
n	30	340	370	n	65	124	558
Mean	449.7	132.8	158.5	Mean	1013.0	870.5	349.4
SD	810.9	671.2	687.8	SD	1524.6	3445.1	996.0
Median	88.0	24.5	28.0	Median	512.0	185.95	66.0
95th percentile	2447.4	216.4	451.0	95th percentile	3986.0	2463.2	1543.9
% <125 ng/L		84		% <125 ng/L		44	
% < 450 ng/L	74			% < 450 ng/L	48		

B. HF Patients – RAMP Results (ng/L)

Age (years)	>75	≤75	ALL
N	80	203	283
Mean	4970.1	3133.1	3652.4
SD	5185.8	3755.0	4280.2
Median	3300.5	1735.0	2040.0
95th percentile	19005.0	11373.3	12800.0
% >125 ng/L		89	
% >450 ng/L	100		

BIBLIOGRAPHY

1. Hall C. Essential biochemistry and physiology of (NT-pro)BNP. Eur J Heart Fail. 2004;6:257-260.
2. Richards AM, Nicholls GM, Yandle TG, et al. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: New hormonal predictors of left ventricular function and prognosis after myocardial infarction. Circ. 1998;97:1921-1929.
3. Rademaker MT, and Richards MA. Cardiac natriuretic peptides for cardiac health. Clin Sci. 2005;108:23-36.
4. Januzzi JL, Camargo CA, Anwaruddin S, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. Am J Cardiol. 2005;95:948-954.
5. Baggish AL, Cameron R, Anwaruddin S, et al. A clinical and biochemical critical pathway for the evaluation of patients with suspected acute congestive heart failure. The proBNP investigation of dyspnea in the emergency department (PRIDE) algorithm. Crit Path Cardiol. 2004;3:171-176.
6. James SK, Lindahl B, Siegbahn A, et al. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a global utilization of strategies to open occluded arteries (GUSTO)-IV substudy. Circ. 2003;108:275-81.
7. Jernberg T, Stridsberg M, Venge P, et al. N-terminal pro brain natriuretic peptide on admission for early risk stratification of patients with chest pain and no ST-segment elevation. J Am Coll Cardiol. 2002;40:437-45.
8. Fisher C, Berry C, Blue L, et al. N-terminal pro B type natriuretic peptide, but not the new putative cardiac hormone relaxin, predicts prognosis in patients with chronic heart failure. Heart. 2003;89:879-81.
9. Schnabel R, Rupprecht HJ, Lackner KJ, et al. Analysis of N-terminal-pro-brain natriuretic peptide and C-reactive protein for risk stratification in stable and unstable coronary artery disease: Results from the AtheroGene study. Eur Heart J. 2005;26:241-249.
10. Kragelund C, Groenning B, Kober L, et al. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. N Eng J Med. 2005;352:666-675.
11. Ndrepepa G, Braun S, Niemoller K, et al. Prognostic value of N-terminal pro-brain natriuretic peptide in patients with chronic stable angina. Circ. 2005;112:2102-2107.

Formatted: German (Germany)

Formatted: Italian (Italy)

Formatted: English (U.S.)

Formatted: Dutch (Netherlands)

Formatted: Dutch (Netherlands)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

Response Biomedical Corporation
c/o Dr. Ken Pilgrim, Director – Quality/Regulatory
1781 – 75th Avenue W.
Vancover, British Columbia
Canada V6P 6P2

JUL 21 2008

Re: K063662
Trade/Device Name: Response Biomedical Corporation RAMP® NT-proBNP Assay
Regulation Number: 21 CFR 862.1117
Regulation Name: B-type Natriuretic peptide test system
Regulatory Class: Class II
Product Code: NBC
Dated: April 22, 2008
Received: April 23, 2007

Dear Dr. Pilgrim:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820).

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific information about the application of labeling requirements to your device, or questions on the promotion and advertising of your device, please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at (240) 276-0490. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (240) 276-3150 or at its Internet address at http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Jean M. Cooper, M.S., D.V.M.

Jean M. Cooper, M.S., D.V.M.
Director
Division of Chemistry and Toxicology
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and
Radiological Health

Enclosure

Statement of Indications for Use

Indications for Use

510(k) Number (if known): K063662

Device Name: RAMP® NT-proBNP Assay

Indications for Use:

The RAMP NT-proBNP Assay is a quantitative immunochromatographic test indicated for use as an *in vitro* diagnostic product used to measure N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in EDTA whole blood. Measurement of NT-proBNP aids in the diagnosis and assessment of severity in individuals suspected of having heart failure and may aid in the risk stratification of patients with heart failure.

Prescription Use X (21 CFR Part 801 Subpart D) And/Or Over the Counter Use ____. (21 CFR Part 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE; CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD)

Jean Cooper

Division Sign-Off
Office of In Vitro Diagnostic Device
Evaluation and Safety

510(k) K063662